REMARKS

In a non-final Office Action mailed December 5, 2006, the Examiner in charge of the above-identified application objected to and rejected the claims for a variety of reasons. Applicants respond below to the issues presented in the Office Action. In view of the amendments noted above and the arguments presented herein, applicants respectfully request reconsideration of the merits of this application.

Applicants thank Examiner Christopher Gross and Supervisor Epperson for conducting a telephonic interview on February 2, 2007 with Professor Robin L. Polt, Dr. Mary Louise Trammell and the applicants' undersigned representative to clarify issues related to priority and obviousness recited in the first Office Action. Applicants have reviewed the Interview Summary mailed on February 27, 2007 and are generally in agreement with its contents. To address the issues discussed at the Interview, applicants submit the amendments above, arguments set forth herein below, and the enclosed Declaration under 37 CFR 1.132 of Professor Robin L. Polt along with Exhibit A (his *curriculum vitae*). Based on this submission, applicants respectfully request reconsideration and withdrawal of all the rejections set forth in the Office Action.

Priority

The Office Action asserts that the prior-filed provisional application, Application No. 60/449,989 filed on 02/25/2003, fails to provide adequate support or enablement under 35 U.S.C. 112, 1st paragraph for one or more claims of this application. Specifically, it is asserted that the provisional application discloses only one disaccharide species (i.e., YtGLFS (β-maltose)) although the instant claims are broader in scope. Also, the Examiner asserts that the provisional application does not disclose packages of injectable pharmaceuticals as set forth in Claims 9 and 10. Therefore, the priority date recognized by the USPTO for the claims of this application is 2/24/2004.

Applicants disagree with this characterization of the provisional application. Applicants submit the provisional teaches that the enkephalin analogues provide a much better analgesic effect when a disaccharide is attached to it (*see* pg. 2, 2nd para.). As support, the provisional application discloses at least two species of disaccharides: maltose and lactose, which can be found, for example, at pgs. 1 and 2 of the specification.

As to the recitation of "packages of injectable pharmaceuticals" in Claims 9 and 10, applicants submit any reference to such packages is deleted from the claims and the objection is now moot. Thus, applicants believe that this application is properly entitled to claim the priority date benefit of U.S. provisional application 60/449,989.

Claim Amendments

Claims 1, 3, 4, 7-11 are amended hereinabove to more clearly define the nature of the claimed embodiments. Specifically, Claim 1 is amended to define the components of the glycosylated enkephalin: (1) the message sequence and (2) the transport sequence with disaccharide selected from the group consisting of lactose, maltose and melibiose. Claims 4 and 7-10 require that the glycopeptides be capable of passing across the blood brain barrier (BBB). These claims further define the structure of the glycosylated peptide, such as the disaccharides, the amino acid residues, and their stereochemistry. The preamble of Claim 7 is amended to delete the phrase "drug delivery package labeled for use as a human drug, the package containing a." This amendment to the preamble renders moot all art-based rejections cited in the present Office Action relating to a drug delivery package. The limitations of new Claim 11 mirror those of Claim 1. Claims 2 and 5-6 are believed redundant in view of the amended claims and are canceled without prejudice or disclaimer. Also, new Claim 12 mirrors Claim 11, except the term D-amino acid is intended to encompass any D-amino acid at the 2nd position after tyrosine. Support for these claim amendments is found, for example throughout the specification, specifically at pg. 5, [00018] through pg. 6, [00022]; pg. 7, [00028]; and pg.10, Table 2. No new matter is added by the introduction of these claims. In view of these amendments, applicants respectfully request that the rejections be reconsidered and withdrawn.

Claim Rejections - 35 USC §112

Claims 3 and 5-6 stand rejected under 35 U.S.C. 112, 2nd paragraph, as being indefinite. The Examiner asserts that Claim 3 recites vague and indefinite language in the molecule designated "MMP2005" in Table 2. In response, applicants amend Claim 3 to include the structure of the glycosylated enkephalin and the correct ID Code as set forth in Table 2 of the specification as originally filed. Thus, this rejection should be withdrawn.

Next, Claim 5 is rejected for indicating the disaccharide is located on the address region of the peptide. The Examiner asserts the disclosure does not succinctly point out the metes and bounds of the "address region." Applicants disagree. It is submitted that the address region, also known as the transport sequence is clearly described in the specification (see pg. 10, Table 2; pg. 5, para. 19-20; and pg. 6, para. 22). For clarification purposes, Claims 5 and 6 are canceled and their contents is incorporated into Claims 1 and 11. As such, this rejection is believed to have been overcome.

Claim Rejections 35 USC §102

Claims 4-7 stand rejected under 35 U.S.C. 102(b) as being anticipated by Horvath et al. (1986) *Synthesis* 3:209-211 as evidenced by Egelton et al. (2001) *J. Pharmacology and Experimental Therapeutics* 299:967-972. Specifically, the Examiner asserts that Horvath et al. teach especially in compounds 8a-f, a method of preparing enkephalin disaccharide pseudoureas. Applicants traverse the rejection.

Applicants submit that Horvath is an improper reference because it does not disclose each and every element set forth in the amended claims as required by MPEP §2131. Horvath does not disclose applicants' claimed peptide sequence. Horvath is a chemical synthesis paper relating to neoglycopeptides or derivatives of Leu-enkephalin (a naturally occurring pentapeptide), not glycopeptides. In contrast, applicants' glycosylated enkephalins are hexapeptides with a Serine for attachment of the β-disaccharide. In Horvath, it is unclear to which amino acid the glycoside (acyl sugar) is attached to in the neoglycopeptide as Horvath does not have a Serine to facilitate the β-O-linkage. Thus, Horvath does not disclose each and every element of the claimed embodiments, and cannot anticipate applicants' claims.

Furthermore, applicants believe that Horvath is not an enabling disclosure under MPEP §2121.01. First, Horvath does not disclose the claimed species of disaccharides. Second, nowhere in Horvath does it discuss opioid binding, pharmacology or any effects on the bio-distribution of these compounds on the blood-brain barrier (BBB). Thus, since the compounds disclosed by Horvath are both structurally and functionally different from the claimed glycopeptides, the rejection should be withdrawn.

The Examiner also asserts that Egleton teaches that glycosylation improves passage through the BBB and that this property of crossing the BBB (set forth in Claim 4) is inherent in the peptides disclosed in Horvath. Again, applicants disagree.

As evidence that Horvath and Egleton cannot be combined to arrive at applicants' invention, applicants submit herewith a Declaration by Professor Robin L. Polt. Dr. Polt's Declaration is intended to show that the claimed process and products are not inherent in the documents cited by the Examiner, as the claims yield unexpectedly superior results above and beyond the contents of the cited documents.

In the Declaration, Dr. Polt asserts that Egleton does not cure the deficiencies of Horvath. Egleton simply defines the general state of the art and is not considered to be particularly relevant. Egleton shows that opioid peptides glycosylated with a monosaccharide (i.e., glucose) exhibit improved BBB penetration. No sugar other than glucose is disclosed in Egleton. Thus, Egleton is silent on the effect of other monosaccharides on BBB penetration. More importantly, Egleton is silent on the unexpectedly superior results that disaccharides, such as lactose, maltose and melibiose have on the claimed enkephalin peptides. The combination of Egleton and Horvath is not sufficient to predict that surprisingly superior analgesic and BBB penetration results could be obtained with the claimed combination of message and address. Applicants' claimed combination was not obvious in view of the cited art.

As to the Examiner's inherency rejection applicants note that improved penetration of BBB does not *necessarily flow* from glycoslated enkephalin peptides. It is well known that:

> "To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991)."

Applicants submit that improved analgesic effect and penetration of BBB does not necessarily flow from all glycoslated enkephalin peptides. At best, the results are mixed. Applicants have observed that very similar enkephalin peptides such as the following:

> YtGFLS(β-D-Glc)S(β-D-Glc), where "t" is a D-Threonine and "S" is an L-Serine;
> YtGFLs (β-D-Glc), where "t" is a D-Threonine and "s" is a D-Serine; and
> YsGFLt (β-D-Glc), where "s" is a D-Serine and "t" is a D-Threonine

show very potent binding to opiate receptors, yet fail to show enhanced central activity, presumably due to their failure to penetrate the blood-brain barrier. Accordingly, penetration of the BBB is not an inherent property of all glycosylated enkephalin peptides. In view of these claim amendments and comments, it is respectfully requested that the rejection be respectfully reconsidered and withdrawn.

Claims 1 and 4-7 stand rejected under 35 U.S.C. 102(b) as being anticipated by Mitchell et al. (2001) *JOC* 66:2327-2342. The Examiner asserts that Mitchell teaches, especially in the abstract and scheme 7, preparation of O-linked enkephalin glycopeptide analogs comprising the amino acid sequence YcGF, which reads on Claims 5 and 6. Applicants respectfully disagree.

Applicants submit that Mitchell discloses the synthesis of O-linked glycopeptides. However, the peptides synthesized in Mitchell are of a different class of enkephalins. The message segment of the peptide (pharmacophore) disclosed in the abstract and page 2336 of Mitchell is structurally different from the message portion of applicants' claimed peptides. Mitchell's peptide pharmacophore shows two cysteines forming a disulfide linkage. Such disulfide linkages are known to the skilled artisan to be problematic because the disulfides react with proteins and cause immunogenic side effects. As such, applicants believe that Mitchell's peptides are not useful as analgesic compounds. Mitchell's peptides are simply tools designed to probe the significance of the glycoside moiety and the carbohydrate-peptide linkage region in BBB transport, not for actually delivering analgesia to an individual in need thereof. Thus, Mitchell does not disclose each and every element of the claimed embodiments, and cannot anticipate applicants' claims.

Claims 1, 4-5 and 7 stand rejected under 35 U.S.C. 102(b) as being anticipated by Elmagbari et al. (2001) FASEB Journal 15:pA915, Abstract. The Examiner asserts that Elmagbari teaches antinociceptive potency (a measure of analgesia per figure 1 of the instant specification), which is enhanced when enkephalin peptides are O-linked with β-lactose (a disaccharide). Applicants respectfully disagree.

Again, applicants submit that Elmagbari is an improper reference because it does not disclose each and every element set forth in the amended claims as required by MPEP §2131. Elmagbari is an abstract that generically summarizes the effect of bis and tris monosaccharides and a trisaccharide (malotriose) on structure-activity requirements for BBB

transport and receptor binding of the enkephalin-based opioid glycopeptides. The abstract refers to β-lactose, but does not disclose the amino acid sequence for the message portion of the peptide to which the lactose is allegedly linked. Elmagbari provides no structural reference for the "message portion" of the enkephalin-based opioid peptides which is a claimed element.

Furthermore, applicants believe that Elmagbari does not enable a skilled artisan to arrive at the claimed invention as required in MPEP §2121.01. Nowhere in Elmagbari does it mention anything about the message sequence. Based on what is disclosed, it would require a skilled artisan undue effort and experimentation to design the claimed peptides, evaluate their analgesic effect and their efficiency of transport across the BBB. Since Elmagbari does not recite each and every element as set forth in the claims and does not contain an enabling disclosure, the rejection is unsupported and should be withdrawn.

Claims 1-2, 4-7 and 10 stand rejected under 35 U.S.C. 102(a) as being anticipated by Palian (2003) JACS 125:5823-5831. The Examiner asserts that Palian teaches throughout the document and especially the abstract and scheme 1, a method for preparing enkaphalin analogs comprising the amino acid sequence YtGFLS-amide O-linked to β-maltose. Applicants disagree with the rejection.

At the outset, applicants submit that Palian is an improper reference as it does not anticipate applicants' claims. Palian's article was published electronically on the Web on April 22, 2003. Applicants' provisional application was filed on February 25, 2003. Therefore, applicants' provisional application predates the earliest public disclosure from Palian.

Furthermore, applicants submit that Palian is an improper reference because it does not disclose each and every element set forth in the amended claims as required by MPEP §2131. Palian examines the conformations of a series of four glycosylated enkephalin analogues in the presence and absence of micelles. In the abstract, Palian recites that "Glycopeptide 2 *[bearing the monosaccharide β-glucose]* has been previously reported to penetrate the blood-brain barrier (BBB), and produce potent analgesia superior to morphine in mice (*J. Med. Chem.* (2000), 43, 2586-90 and *J. Pharm. Esp. Ther.* (2001), 299, 967-972)." Palian does not indicate that out of the four enkephalin analogues, glycopeptide #3, bearing the disaccharide β-maltose exhibits BBB transport properties superior to monosaccharides.

In fact, Palian's CD (circular dichroism) analysis shows that the various glycosylated enkephalin compounds tested are quite similar and it is impossible to differentiate between the various glycopeptide conformations (*see* pg. 5825-5826). Thus, there is no suggestion that glycopeptide #3 (bearing β-maltose) would show superiority in providing analgesia or BBB transport. As such, applicants believe that Palian does not anticipate the claimed invention and the rejection should be withdrawn.

Claim Rejections - 35 USC §103

Claims 1-9 stand rejected under 35 U.S.C. 103(a) as being unpatentable over either of Roques et al. (US Patent 4,407,794) in view of Mitchell et al. (2001) *JOC* 66:2327-2342. Applicants respectfully disagree with the rejection.

As evidence of non-obviousness, applicants again refer to Dr. Polt's Declaration. Dr. Polt's Declaration is intended to show that the claimed process and products are not obvious in view of the documents cited by the Examiner, as the claims yield unexpectedly superior results above and beyond the contents of the cited documents.

Applicants submit that Roques does not teach, suggest nor motivate one of ordinary skill in the art to arrive at the claimed invention. In the Declaration, Dr. Polt asserts that Roques discloses a variety of penta- and hexa- peptide derivatives which act on opiate receptors to provide analgesia. In Table 1, Formula No. 4, Roques also appears to disclose a peptide backbone similar to that of an embodiment of the claimed invention. Roques does not disclose O-linked disaccharide enkephalin derivatives or any kind of glycosylation. In fact, as indicated in the Declaration, Roques' compounds have no utility as pharmaceuticals due to their poor biodistribution and inability to penetrate the BBB to reach the opiate receptors in the brain. Thus, Roques does not teach nor suggest the claims.

Furthermore, as indicated in Dr. Polt's Declaration, Mitchell does not cure the deficiencies of Roques. Mitchell discloses a different class of enkephalins, which have a different (even unfavorable) peptide sequence. Specifically, the message segment of the peptide (pharmacophore) disclosed in both the abstract and the body of Mitchell (see pg. 2336) is structurally different from the message portion of the claimed peptides. Mitchell's peptide pharmacophore shows two cysteines forming a disulfide linkage, which is known to the skilled artisan to be problematic because it reacts with proteins and causes immunogenic

side effects. As such, applicants believe that Mitchell's peptides are not useful and to some extent teach away from applicants' novel and surprisingly inventive analgesic compounds. Mitchell's peptides appear to be tools designed to probe the significance of the glycoside moiety and the carbohydrate-peptide linkage region in BBB transport. Thus, it would not have been *prima facie* obvious for one of ordinary skill in the art, at the time the claimed invention was made to combine the teachings of Roques and Mitchell to render obvious the claimed invention.

Applicants believe that this is a classic "obvious to try" type of rejection. However, "obvious to try" is not the standard of 35 U.S.C. §103. While it may or may not have been obvious to try to combine the teachings of the cited art to arrive at the present invention, applicants believe there was insufficient data available to predict the outcome of this work prior to the data disclosed in this patent application. The art of modifying enkephalin to achieve analgesia and BBB transport is less than predictable art. While certain types of modifications to enkephalins are known, it is not predictable in advance which modifications will increase this without adversely affecting the other properties of the enkephalin. Furthermore, there was no reasonable expectation of success in this approach because the result is highly specific. Again this could not have been predicted in advance. Thus, the cited art alone or in combination provide no motivation to arrive at applicants' claims.

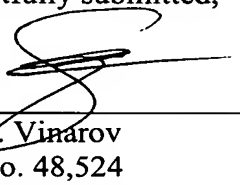
It appears the Examiner may have impermissibly used "hindsight" to reject the claims. Specifically, the Examiner inadvertently used applicants' teaching as a blueprint to look through Roques and Mitchell to piece together elements therein to defeat the patentability of the claimed embodiments. This type of examination is unreasonable and prohibited by the MPEP 2142. In view of these remarks, applicants respectfully request reconsideration of this rejection as applied to the rejected claims.

Accordingly, applicants respectfully request that in view of these claim amendments and remarks, the rejection be respectfully reconsidered, withdrawn and that a timely Notice of Allowance be issued in this case.

No fee is believed to be due. However, if any fee is due or any extension of time is required in this or any subsequent response, please consider this to be a petition for the

appropriate extension and a request to charge the petition fee to the Deposit Account No. 17 0055.

Respectfully submitted,



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